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Influence of Hypophysectomy on Dopamine Receptors and Dopaminergic Behaviors

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HRUSKA, R. E. *Influence of hypophysectomy on dopamine receptors and dopaminergic behaviors.* PHARMACOL BIOCHEM BEHAV 27(4) 629–633, 1987.—Hypophysectomy (Hypox) has been proposed to alter the behavioral and biochemical indices of striatal dopamine (DA) function. Since the regulation of striatal DA receptors by hormones may involve the pituitary, it was relevant to reevaluate the effects of Hypox in male and female rats. Behaviorally, dopaminergic agonists exerted enhanced activity in Hypox male and female rats. It has been suggested that these changes are due to altered metabolism since no increase in the DA receptor populations was observed. Dopaminergic antagonists showed equivalent behavioral actions in male and female rats, whether intact or Hypox. Biochemically, neither the density nor the affinity of the striatal DA receptors is altered by Hypox in female rats for 1–2 weeks or male rats for 5–6 weeks. However, in female rats at 5–6 weeks after Hypox there is a significant decrease in receptor number. This decrease in density is not reflected in behavioral changes to either DA receptor agonists or antagonists. Therefore, all dopaminergic behavioral changes do not result from alterations in DA receptors and changes in DA receptors do not necessarily dictate altered behavioral responses to dopaminergic agents.

Hypophysectomy Dopamine receptors Striatal dopamine receptors

RECENTLY, the regulation of striatal dopamine (DA) receptors and striatal dopaminergic functions by the pituitary has generated much interest [6, 7, 9, 11, 13, 14, 16, 18]. Before drug-induced changes in striatal DA function can be evaluated, it is necessary to determine the role of endogenous pituitary hormones on normal striatal DA function. The easiest direct means of such a test is the removal of the pituitary (hypophysectomy, Hypox) and the subsequent measurement of striatal DA function.

Reports which monitored behaviors mediated by striatal DA receptors have found in most instances that these types of behaviors are not altered or are increased by Hypox [10, 16, 19, 25]. It has been suggested that the increased behavioral responses in Hypox rats are due to altered metabolism of the administered drugs [19]; however, more drug may not enter into the brain [1].

Direct measurements of striatal DA receptors in Hypox rats have been variable and reports have indicated no change [11, 13–16], a 15–29% decrease [4,5], or a 36–69% increase [10,25]. Because of the variability of the changes reported for striatal DA function after Hypox and the importance of this change for DA receptor regulation, it was imperative that DA function in the striatum be reevaluated before additional studies were performed.

METHOD

The following groups of Sprague-Dawley rats were obtained from Taconic Farms, Germantown, NY: intact males, sham-Hypox males, Hypox males, intact females, ovariectomized (Ovx) females, Hypox females, and Ovx+Hypox females. All rats weighed 200–225 g when received and were maintained for 1 to 6 weeks. Most of the surgical procedures were performed several days before shipment, allowing the partial verification of the surgical procedures by weight loss and the partial restoration of the rats' health.

Upon receipt the Hypox rats were immediately given special attention. They were housed in plastic cages with sawdust bedding. This type of cage assists in the avoidance of room air drafts and the bedding helps in retention of body heat. The sham-Hypox, Hypox, and Ovx+Hypox groups were given immediate and continuous access to a drinking solution containing 5% dextrose, 203 mg% NaCl, 8.3 mg% KCl, 3.5 mg% $CaCl_2$, and 1.7 mg% $MgCl_2$. The other rats received free access to tap water.

For behavioral and biochemical testing the rats were maintained for either 1–2 weeks or 5–6 weeks from the date of surgery.

Behavioral measurements included stereotyped and cataleptic behaviors. Stereotyped behavior was rated in rats two ways. In one experiment a classical 4 point rating scale was used, as previously described [12]. The rats were monitored for 60 seconds for the presence of the following behaviors: 0—sleeping or normal locomotion; 1—sniffing; 2—licking, gnawing, or biting; 3—same as 2 but also lack of locomotion; and 4—tremors. Rats were injected with apomorphine hydrochloride (4 mg/kg, IP) and evaluated 30 min after the injection.

In the second experimental design, each rat was rated for 60 sec (in 6 blocks of 10 sec) for the presence (not necessarily continuously) of locomotor activity, rearing, sniffing, or oral behavior. Each behavior was rated separately from 0 (no

observation of that behavior) to 6 (present in each 10 sec block), with no attempt to discern intensity of the behavior. The results are expressed as a percent of the maximal response attainable. In this design, rats were injected with apomorphine hydrochloride (2 mg/kg, IP) and evaluated everv 10 min for the duration of the behaviors.

Cataleptic behavior was evaluated as previously described [3], using the dopamine receptor antagonist, haloperidol. Intact and Hypox male rats were evaluated for akinesia, hanging, and clinging, as timed by stopwatch after the injection of haloperidol at a dose of 1.0 or 2.0 mg/kg, IP. The test after 1.0 mg/kg was made at 60 min after haloperidol injection, while the test after 0.2 mg/kg was made every 30 min for 150 min. Akinesia was assessed as the time it took the rat to move three of its four paws after being placed on a flat open surface (maximum of 60 sec). Hanging was measured after placing the rat's forelimbs over a 2 mm diameter bar elevated 10 cm above the floor. Hanging was assessed until the rat moved off the bar (maximum of 60 sec). Clinging was measured on two parallel bars elevated 10 and 23 cm from the floor of the apparatus, each bar being 2 mm in diameter. The rat was placed with its front paws on the upper bar and its hindpaws on the lower bar. Clinging was assessed as the time for the rat to move one paw to the other bar of fall from the bars (maximum of 120 sec).

For biochemical assays the rats were decapitated, their brains removed and placed into ice-cold saline. The brains were dissected reproducibly using a plastic block. Each brain was sliced in the frontal plane at the stereotaxic coordinates [17] of A: 8.8 and 6.8 mm, yielding a 2 mm thick slice through the anterior striatum. The anterior cut was at level of the posterior border of the nucleus accumbens and the posterior cut was at the level of the crossing of the anterior commissure. The slice was placed flat on a glass plate on ice, the tissue below the anterior commissure discarded, and the striatal tissue dissected by forceps from the lateral ventricle to under the corpus callosum in about a 180° arc. The tissue was either used immediately or frozen at −80°C for 1–2 weeks.

The striatal tissues from both sides of one rat brain (about 40 mg tissue) were placed into 4 ml of ice-cold assay buffer (81 mM Na_2HPO_4, 19 mM KH_2PO_4, pH 7.4) and homogenized with a Tissumizer (Tekmar) with a 10 mm diameter generator at 65% of maximal power for 10 sec. The suspension was centrifuged at 40,000 × g for 10 min, the supernatant discarded, 4 ml of fresh buffer added, the pellet rehomogenized, and this procedure repeated again. The final homogenate was stored on ice until used, usually within 2 hour, in the binding assay. Aliquots of tissue homogenate (100 μl) were saved for protein analyses [20] using BSA as the standard.

The D_2 DA receptor assay has been described previously [11–15]. Because of the sensitivity of the assay, the striatal tissue from each rat was analyzed separately. Briefly, the assay was performed in 10 ml (final volume) of assay buffer. Specific binding was defined as the differences between total binding and non-specific binding, which was determined in the presence of 0.5 μM d-butaclamol. The binding of [^{3}H]spiperone, added in increasing concentrations from 3 to 100 pM, was used to label D_2 DA receptors. Incubation was performed at 37°C for 30 min and terminated by rapid filtration through GF/B filters. Quantitation was by standard liquid scintillation counting procedures. The density and affinity were determined by least-squares linear regression analyses of Scatchard [28] plots.

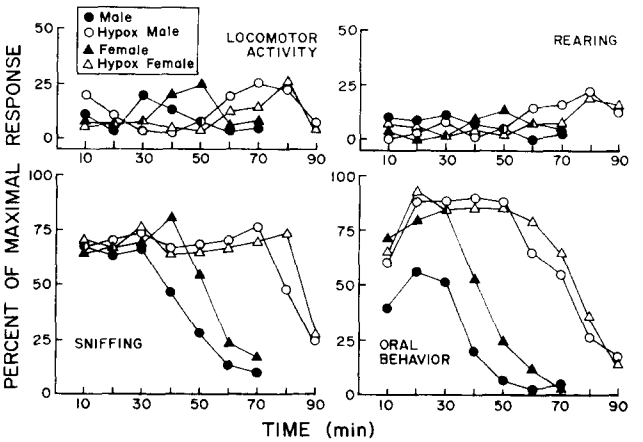

FIG. 1. Stereotyped behavior produced by apomorphine (2 mg/kg, IP) after 1 to 2 weeks of Hypox. Each value is the mean of 10 male or female or 11 Hypox male or Hypox female rats. ANOVA indicated no significant difference in locomotor activity, $F(3,266)=1.2$, or rearing, $F(3,266)=0.5$. Sniffing was increased in Hypox male rats, $F(1,133)=22$, $p<0.005$, and in Hypox female rats, $F(1,133)=5.1$, $p<0.05$, and oral behavior was increased in Hypox male rats, $F(1,33)=93$, $p<0.005$, and in Hypox female rats, $F(1,133)=38$, $p<0.005$, each group compared to the respective intact male or female group. Oral behavior was also increased in intact female rats compared to intact male rats, $F(1,126)=16$, $p<0.005$.

In some experiments the concentration range of [^{3}H]spiperone was extended from 3 pM to 2 nM in order to perform a two-site analysis of the binding data. The BDATA program of EMF Software was used to evaluate the data from each 15-point saturation analysis.

Successful Hypox was verified by three procedures, failure at any one criterion was sufficient reason to remove the values from further analyses. First, the weight of each rat was measured. Our diet of 5% dextrose in the drinking solution helped Hypox rats to remain healthy, but even with this treatment Hypox rats either maintained a constant body weight or lost a small amount of body weight. Therefore, the data from any Hypox rat which gained body weight was discarded. Second, at decapitation the skull was inspected visually to insure removal of the pituitary. Also, the base of the brain was examined for additional damage. If any pituitary fragment remained or the brain (hypothalamic area) suffered any damage, the data from that rat was discarded. Third, at decapitation the trunk blood was collected and analyzed for prolactin using the standard (RP-2) and specific antibody provided by the National Pituitary Agency. Prolactin is a pituitary hormone which should be absent in Hypox rats. If prolactin was present, the data from that rat was discarded.

RESULTS

Behavioral Tests

Stereotyped behavior to apomorphine (4 mg/kg, IP) was compared in intact and Hypox male rats at one to two weeks after surgery. At 30 min after injection the rating scale score of the intact male rats (N=11) was 1.09±0.34, while that of the Hypox male rats (N=11) was 2.27±0.30, a significant increase by Mann-Whitney U-test [30], $p<0.05$. The intact rats exhibited mostly sniffing, while the Hypox rats exhib-

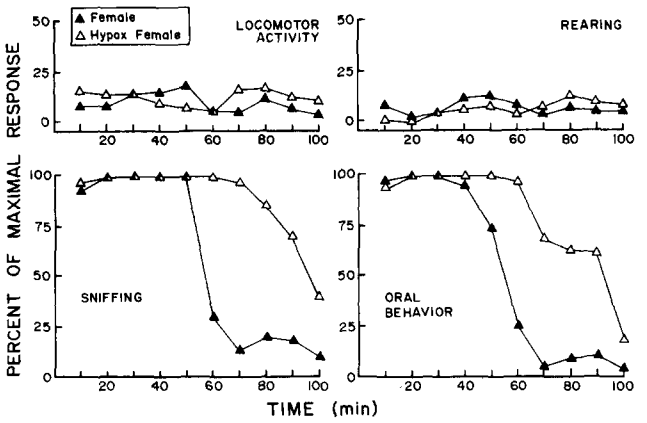

FIG. 2. Stereotyped behavior produced by apomorphine (2 mg/kg, IP) after 5 to 6 weeks of Hypox. Each value is the mean of 10 female or 12 Hypox female rats. ANOVA indicated no significant difference in locomotor activity, $F(1,200)=1.6$, and rearing, $F(1,200)=1.2$. Both sniffing, $F(1,200)=108$, $p<0.005$, and oral behavior, $F(1,200)=96$, $p<0.005$, were significantly increased.

TABLE 1

EFFECT OF HYPOPHYSECTOMY ON DOPAMINERGIC BEHAVIORS

Group	Catalepsy Score†
	akinesia (sec)
Intact or Sham-Hypox male*	25.1 ± 8.8
Hypox male	41.1 ± 5.8
	hanging (sec)
Intact or Sham-Hypox male*	28.0 ± 8.7
Hypox male	23.3 ± 8.3
	clinging (sec)
Intact or Sham-Hypox male*	91.0 ± 18.8
Hypox male	119.0 ± 1.0
	composite (%)
Intact or Sham-Hypox male	54.8 ± 14.9
Hypox male	68.8 ± 10.2

*The times (sec) for the Intact (N=4) and Sham-Hypox (N=3) groups were 23 and 28 for akinesia, 33 and 21 for hanging, and 93 and 89 for clinging, respectively.

†Values are the mean ± SEM of 7 individual observations.

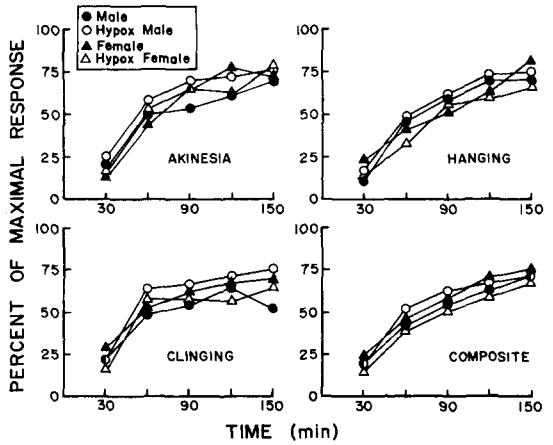

FIG. 3. Cataleptic behavior produced by haloperidol (0.2 mg/kg, IP) after 1 to 2 weeks of Hypox. Each value is the mean of 8 rats. ANOVA indicated no significant difference in any parameter, $F(3,140)=0.6$ for akinesia, 1.8 for hanging, 1.1 for clinging, and 1.3 for composite score.

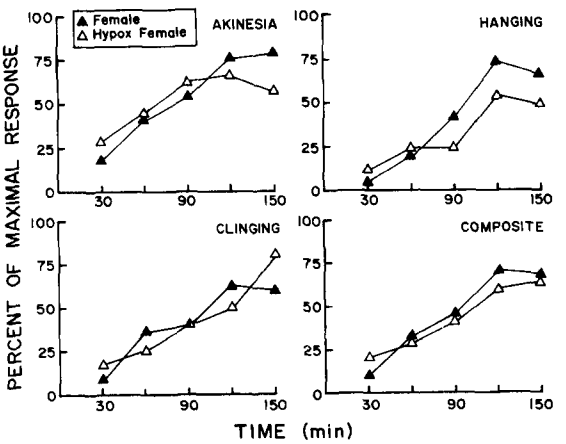

FIG. 4. Cataleptic behavior produced by haloperidol (0.2 mg/kg, IP) after 5 to 6 weeks of Hypox. Each value is the mean of 10 rats. ANOVA indicated no significant difference in any parameter, $F(1,90)=0.6$ for akinesia, 1.4 for hanging, 0.3 for clinging, and 0.9 for composite score.

ited mostly oral behaviors such as licking, gnawing, or biting.

These observations were extended to male and female, intact and Hypox rats over a time course and using a frequency of occurrence measurement. At one to two weeks after surgery the rats were treated with apomorphine (2 mg/kg, IP). Neither locomotor activity nor rearing were different between male and female rats or between intact and Hypox rats of either sex (Fig. 1). Sniffing and oral behavior were increased in Hypox rats of either sex and the increase was primarily in the duration over which the behavior was observed rather than its frequency.

A separate group of female rats was tested at about 5 weeks after surgery. Again the intact and Hypox female rats displayed equivalent amounts of locomotor activity and rearing, while in Hypox female rats both sniffing and oral behavior were increased (Fig. 2).

Cataleptic behavior to haloperidol (1 mg/kg, IP) was evaluated in intact, sham-Hypox, and Hypox male rats 1 week after surgery. Since the intact and sham-Hypox groups were equivalent, these data were combined. The Hypox group exhibited equivalent amounts of cataleptic behavior at 60 min after injection in all three measurements and the composite score (Table 1).

Cataleptic behavior was also measured over a time course using a lower dose of haloperidol (0.2 mg/kg, IP). When using rats one to two weeks after surgery, neither male and female nor intact and Hypox rats of either sex exhibited any significant difference in any of the cataleptic behavior measurements or the composite score (Fig. 3).

TABLE 2

D_2 DA RECEPTORS IN THE STRIATUM OF RATS

Experiment	Group	N	Kd(pM)	Bmax (fmole/ml) prot)
1	Male, Intact	11	12.0 ± 1.3	335 ± 9
(1–2 weeks)	Male, Hypox	10	12.5 ± 0.6	324 ± 6
2	Female, Intact	12	13.0 ± 1.5	326 ± 23
(1–2 weeks)	Female, Hypox	6	15.1 ± 1.2	314 ± 16
	Female, Ovx	7	14.4 ± 1.1	327 ± 21
	Female, Ovx+Hypox	9	15.2 ± 1.9	316 ± 17
3	Male, Intact	9	19.0 ± 3.3	360 ± 33
(5–6 weeks)	Male, Hypox	9	18.5 ± 2.1	356 ± 30
	Female, Intact	17	19.0 ± 1.9	370 ± 19
	Female, Hypox	21	16.6 ± 1.4	293 ± 14*
4	Female, Intact	6	10.5 ± 0.6	316 ± 8
(5–6 weeks)	Female, Ovx	6	10.7 ± 1.3	318 ± 20

*20.8% Decrease, significant at $p<0.005$ compared to Female, Intact group.

A separate group of female rats was tested 5 to 6 weeks after surgery with the low dose of haloperidol (0.2 mg/kg, IP). Again intact and Hypox female rats showed eqivalent cataleptic behavior in all measurements including the composite score (Fig. 4).

Biochemical Evaluation

The density and affinity of the striatal D_2 DA receptors were evaluated in intact, sham-Hypox, and Hypox male or female rats at either 1 to 2 weeks or 5 to 6 weeks after surgery. The intact and sham-Hypox groups were equivalent, and these data were combined. As shown in Table 2, the apparent affinity of the striatal D_2 DA receptors did not change as compared to each control group in any experiment.

At 1 to 2 weeks after surgery neither the male nor the female Hypox rats exhibited a change in receptor density (Table 2, Experiments 1 and 2). When these measurements were made on rats after 5 to 6 weeks, the Hypox female rats had a significant decrease in D_2 DA receptor density (Table 2, Experiment 3). Female rats which were only ovariectomized had no change in the receptor density (Table 2, Experiment 4).

An attempt was made with the data from Table 2, Experiment 3 to produce a better correlation using two-site analyses. The program was unable to identify the presence of two binding sites from the data.

DISCUSSION

The change in density of striatal D_2 DA receptors is in general agreement with the literature and helps to clear several discrepancies. First, after Hypox, male rats do not show any change in the D_2 DA receptors up to at least 6 weeks. Second, after Hypox, female rats show a time-dependent change which is not associated with estrogens or progesterone since ovariectomy did not replicate the results. Relatively short-term Hypox of female rats does not change the D_2 DA receptors, however, after 5 to 6 weeks there is a 20% loss of density.

An attempt to resolve this loss by two-site analyses failed. In these rats the two sites (the second being the S_2 serotonin receptor) are very difficult to demonstrate in the striatum using [^{3}H]spiperone since the number of S_2 serotonin sites is relatively small (less than 10%) and of lower affinity (more than 20-fold). Under these conditions the contribution of S_2 serotonin binding would be too small to detect using a two-site analysis, as has been suggested previously [22], and would not alter the results of a single-site analysis. Rats of other strains may have different relative densities and affinities of S_2 serotonin and D_2 DA receptors in the striatum. In such cases the two classes of sites may be labeled with [^{3}H]spiperone and separated by two-site analyses of the binding data. However, the present data represent a single class of sites and a loss of striatal D_2 DA receptor density.

At 1 to 2 weeks after Hypox, a time associated with no D_2 DA receptor changes, apomorphine produced a greater stereotyped behavior score and a greater frequency of sniffing and oral behavior. This is consistent with at least 4 reports [1, 10, 19, 25], but disagrees with one report [16] which reported no change. Since that one report used a rating scale and a single time point of 15 min after a SC injection, it is possible that a difference may have been missed.

Since the enhanced stereotyped behavior occurs in Hypox male or female rats without a change in D_2 DA receptors, the effect of Hypox is most likely related to a decreased rate of metabolism of the drug [19]. The role of metabolism is further implicated by the fact that male rats exhibited less oral behavior than female rats and that male rats have the ability to metabolize some drugs more rapidly than female rats (e.g., [23]).

At 1 to 2 weeks after Hypox the cataleptic behavior produced by haloperidol was unchanged. This observation agrees with one report [1], while another report found an increase [19]. It should be noted that in the latter report the male rats were Hypox at a body weight of about 150 g and were probably not mature and had not attained full, adult levels of testosterone before surgery.

Since the biochemical measurements at 5 to 6 weeks after surgery indicated that Hypox female rats had a decrease in D_2 DA receptor density, the behavioral evaluation of a separate group of these rats was performed after the same duration of Hypox. The changes in sniffing and oral behavior as well as cataleptic behavior were qualitatively similar to those observed at 1 to 2 weeks, at a time without D_2 DA receptor changes. Therefore, these behavioral measurements did not reflect the decrease in striatal D_2 DA receptors.

Normally changes in receptor number are associated with changes in behaviors produced by stimulation or antagonism of these receptors. There are two major hypotheses to account for the non-parallel changes in this study. First, the loss of receptors after Hypox represents the loss of nonfunctional receptors, receptors unnecessary for the direct actions of apomorphine or haloperidol. Such receptors could include cryptic (hidden or "silent") receptors as well as presynaptic or autoreceptors.

Second, the major modification of behavior produced by either apomorphine or haloperidol administration is not mediated solely by the D_2 DA receptors in the striatum. The major influence could be contributed by metabolism, diffusion, and so forth, or it could be contributed by D_2 DA receptors in other brain areas. This latter possibility seems remote since the striatum has been demonstrated to be the site for production of stereotyped behavior (particularly sniffing and oral behaviors) and cataleptic behavior [2, 21, 27].

It should be noted that Hypox alters functions other than those associated with postsynaptic DA function in the striatum. Hypox decreases the activity of the enzyme controlling GABA synthesis, glutamic acid decarboxylase [10]. Several striatal functions appear to be independent of pituitary function. Hypox does not alter acetylcholine levels in the striatum [8], presynaptic DA function [29], DA turnover [26], or locomotor activity to repeated electroconvulsive shock [24].

In conclusion, the behavioral responses in Hypox rats should be evaluated carefully, since other effects associated with Hypox may contribute to an enhanced response. An elevated behavioral response to a dopaminergic drug may not be associated with an elevation of D_2 DA receptors. Conversely, a decrease in D_2 DA receptors may not dictate a decreased behavioral response to dopaminergic drugs.

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